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BEHAVIORAL AROUSAL AND NEURAL ACTIVATION AS RADIOSENSITIVE REACTIONS

by
E. L. Hunt
D. J. Kimeldorf

403540

U.S. NAVAL RADIOLOGICAL DEFENSE LABORATORY
SAN FRANCISCO 24, CALIFORNIA

12ND. P7463

PHYSIOLOGY-PSYCHOLOGY BRANCH
D. J. Kimeldorf, Head

BIOLOGICAL AND MEDICAL SCIENCES DIVISION
E. L. Alpen, Head

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Eugene P. Cooper
Eugene P. Cooper
Scientific Director

E. B. Roth, CAPT USN
Commanding Officer and Director

ABSTRACT

In a study designed to detect prompt reactions to ionizing radiation, rats were exposed to 250 kvp X rays and measurements of behavioral departures from sleep and of heart rate were used to indicate activation of the central nervous system. Exposure at a low dose rate (0.25 r/sec) produced a transitory arousal from sleep within the first 12 seconds (accrued dose of 3 r). At a higher dose rate (1.9 r/sec) this initial reaction increased in scope and, by 30 seconds, included also an acceleration in heart rate. Only animals exposed at the higher dose rate exhibited evidence of excitation during the residual period of exposure to a 1,000 r total dose. Accordingly, the intensity of the reaction during exposure depended upon the dose rate rather than the total dose. A transient excitatory effect at the termination of exposure was indicated by the occurrence of behavioral wakefulness for a period of minutes following exposure at both dose rates. The excitatory effects of irradiation were not dependent upon adrenal function since adrenalectomized animals showed a sequence of reactions comparable to that shown by normal animals but with longer latencies. Stimulation through radiosensitive mechanisms apart from the visual receptor system was indicated since ophthalmectomized animals exhibited both behavioral and heart rate responses within seconds after the start of exposure. Some possible modes for the action of ionizing radiation as a stimulus to the nervous system are discussed.

NON-TECHNICAL SUMMARY

The Problem

This investigation was designed to provide information on prompt reactions of the intact mammalian nervous system to low intensity exposure to ionizing radiation.

The Findings

X-ray exposure acts as a stimulus to the nervous system in the rat as evidenced by its power to produce behavioral arousal in the sleeping animal within 12 seconds at an exposure rate of as little as 0.25 r/sec. With exposure at a dose rate of 1.9 r/sec this initial reaction is subsequently increased in scope and includes sub-cortical neural activation as indicated by the presence of a change in heart rate by 30 seconds. Only animals exposed at the higher dose rate exhibited evidence of excitation during the residual period of exposure to a total dose of 1,000 r. Accordingly, the intensity of reaction during exposure depended upon the dose rate rather than the total dose. A transitory excitatory effect at the termination of exposure was also found. Stimulation with X rays did not depend upon adrenal function since adrenalectomized animals showed a similar sequence of reactions. Stimulation through radiosensitive mechanisms apart from the visual receptor system was indicated since blinded animals exhibited both behavioral and heart rate responses within seconds after the start of exposure. The probable basis for the immediate effect is that the nervous system is directly sensitive to ionizing radiation.

CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

INTRODUCTION

A wide variety of techniques have been applied to the investigation of the effects of ionizing radiation on the nervous system, particularly within the last few years (1, 2). Only a few reactions have been found to indicate that the nervous system of the unanesthetized mammal reacts promptly to low dose levels of exposure.

Evidence of early reactions have been obtained from electrographic recordings of brain activity in rats (3, 4), cats (5, 6) and rabbits (7, 8). With radiation doses ranging from 200 to 1,000 r, both cortical and subcortical systems may undergo alterations in spontaneous and evoked activity during the period of exposure (8) or immediately thereafter (5, 6). Phasic alterations in excitability of the mammalian nervous system following extremely low doses of radiation have also been reported in various reviews of the Soviet literature (9-14). Although these alterations in central nervous system function may reflect CNS reactions to abscopal effects of irradiation, more direct

stimulation of the nervous system by ionizing radiation also is possible. Visual stimulation by ionizing radiation under conditions of dark adaptation has long been known to occur (15,16) and very likely is mediated through effects on the photochemical processes of the receptor at energy levels nearly comparable to those required for stimulation with visible light (17-19). Visual sensation in the human has been demonstrated with "flash" exposures of less than a milliroentgen (20), and retinal stimulation in infra-mammalian species has been demonstrated (17) repeatedly (21-23) with electrophysiological measurements.

Behavioral methods have been found to be particularly sensitive for the demonstration of immediate CNS reactions to ionizing radiation. In a number of investigations, recently reviewed (24,25), radiation exposure has been employed as the motivating stimulus in conditioning several species to avoid a gustatory stimulus or to avoid spatial stimuli. In these studies the rat was found to be extremely sensitive to low dose, short duration, whole-body exposure (26); the motivational effect was shown to be independent of direct retinal stimulation (27), and the abdominal region was found to be preferentially sensitive (28). It was concluded that the motivational effects of irradiation were probably produced through humoral mediation and result from radiation effects produced in non-nervous tissues (24). A direct action of radiation on the nervous system, however, could not

be ruled out. In some invertebrates, behavioral reactions to low intensity radiation have been shown to occur with latencies of only a few seconds following the start of exposure (29-32); this is sufficiently rapid to allow the inference of direct stimulation by ionizing radiation. Hug (29,30) has shown in several invertebrate preparations that the response latency is inversely proportional to the intensity of exposure with dose rates above 0.4r/sec. Although these rates of exposure are higher than those required to produce conditioning in the mammal, the presence of a "chronaxie" and of a "rheobase" is consistent with a stimulus-like action for ionizing radiation.

There is a lack of evidence in mammals for reactions with sufficiently short latencies to indicate direct stimulus-like action for ionizing radiation. The present investigation was undertaken to test for the presence of immediate (direct) and delayed stimulus actions of X rays delivered at moderate dose rates. For this purpose, rats in the main series of experiments (Series I) were conditioned to sleep in the exposure situation and measurements were made both of behavioral departures from sleep and of heart rate before, during and following exposure to a 1,000 r dose of hard X rays delivered at either 0.25 or 1.9 r/sec. The occurrence of a response in either variable immediately (within seconds) after the onset of exposure would be indicative of direct stimulation of the nervous system by radiation. Indirect modes of neural stimulation, which might arise from reactions or damage in

abscopal systems, would be reflected in responses made during the residual period of exposure.

Additional experimental series were undertaken as a means of determining the relative importance of certain parameters of the main series. To eliminate possible direct retinal stimulation by radiation the animals in Series II were blinded by complete bilateral ophthalmectomy performed a month before the exposure test. The animals in Series III were adrenalectomized a week before the exposure test to eliminate involvement of adrenal function in the elaboration of irradiation effects found to occur both during (33,34) and immediately following (35-37) exposure. In both series the animals were trained to sleep in the exposure situation to maintain maximum comparability to Series I with regard to the initial state of excitability. Since sensitivity to stimulation would depend upon concurrent nervous activity, this was altered in two additional series of experiments. Normal animals that were not adapted to sleep in the exposure situation were employed in Series IV. These animals were awake at the start of exposure. In Series V experiments the animals were maintained under continuous restraint imposed in a manner designed to promote struggling behavior and to maintain, thereby, a continuously excited state. In both of these series, since the animals remained awake throughout the test period, the behavioral measurement of departures from sleep was inapplicable and only the heart rate measurement was employed.

METHODS AND PROCEDURES

Young adult male Sprague-Dawley rats bred at this Laboratory were used throughout this investigation. Table I shows the animal distribution for each series by treatment group.

The rats were confined to glass chambers for the observations of behavior, for remote recording of heart rate, and for exposure of animals in Series I, II, III and IV. The chamber and the procedures for adaptation used to condition sleep for Series I, II and III, and the general methods employed for recording heart rate in all series have been described previously (38). The restraint employed during the exposure test in Series V was imposed by fastening each rat prone and spread-eagled to a 10 x 12 inch Lucite plate. Each forelimb was encased in a glass tube to prevent biting at the binding that was used to attach each paw to a corner of the plate. To promote struggling a rubber binding was used which allowed the animal to work against an elastic restraint.

A Maxitron (General Electric) X-ray unit, equipped with a lead shutter and operated at 250 kvp and 25 ma. (HVL of 2.3 mm Cu), was used for all irradiations. Before the start of each experiment the dose rate (in air) was measured at the center position within the test chamber (or above the restraining board) by means of thimble dosimetry (Victoreen). For exposure at the high dose rate, nominally 1.9 r/sec, the 1,000 r dose was delivered at a distance of 37 cm in

9 minutes, and in experiments involving exposure at the low dose rate, nominally 0.25 r/sec, the same total dose was delivered at a distance of 104 cm in 67 minutes. Each animal's actual position in the chamber could conceivably range up to $\pm$ 4.5 cm from the centerline position and, correspondingly, the dose rates could range from 1.5 to 2.5 r/sec and from 0.22 to 0.28 r/sec for the high and low rates, respectively. Control animals were located about 100 cm from the tube port behind a 1/4-inch lead plate shield but were otherwise treated like the exposed animals.

Since the effects of stimuli which were coincidental to exposure procedures might be confounded with radiation effects, special precautions were instituted which would limit or control extraneous sources of stimulation. By means of circuit controls, background sounds emanating from the ventilation and water circulating systems were presented without interruption during the entire test session. Also, a heavy sound shield was placed around the shutter device so that it was not possible to detect the sound of the shutter mechanism. Termination of exposure was accomplished silently by shutting off power to the X-ray tube while the shutter remained open and room and machine noises continued.

During the conditioning phase, the animals were adapted to sleep in test chambers which were placed in a large sound-deadened cabinet. A total of 40, 65-75, and 48 hours of adaptation were imposed in Series

I, II and III, respectively, distributed over a week or more before the exposure test. The last adaptation session, and 8-hour period during the day before exposure, was also used to habituate the animals to sounds associated with the exposure test. For this purpose, a magnetic tape recording of X-ray room and machine noise was played repeatedly through a 5-inch speaker located directly in front of the cabinet. This recording was made through a standard crystal microphone located about 18 inches from the tube port and consisted of continuous sounds from the room ventilation system and the X-ray machine water circulation system. As an additional precaution, the sound from the solenoid-actuated shutter mechanism was also incorporated in the recording at aperiodic intervals. During the last adaptation session, the average heart rate value of each animal during sleep was obtained and the rank ordered values within each experiment were used, in conjunction with tables of random premutations, to assign animals to either the exposure or control (lead shielded) group for the next day's test. Since no adaptation sessions preceded the exposure test in Series IV and V, body weight measurements were employed for random assignment to treatment groups.

A standard schedule of procedures and measurements was followed for all experimental runs. From 4 to 8 animals were studied in each run. After their placement in the X-ray room, periodic measurements of heart rate and behavior were made prior to the start of irradiation

over a period of at least two hours in Series I, II and III and of at least 90 minutes in Series IV and V. Rapid sequence recording, which yielded 2 or 3 measurements per minute on each variable for each animal, was started 5 minutes before the shutter was opened and was continued for 10 minutes after the start of exposure. Intermittent measurements were made thereafter at 5-minute intervals to the end of the first half-hour and then at 10-minute intervals to the end of the 2-hour test period.

Behavioral departures from sleep were measured by means of a rating scale. During the X-ray exposure test, the observer viewed each animal through a leaded-glass window to the X-ray room from a distance which ranged from 2 to 5 meters. Mirrors were arranged to provide more than a single angle of view of each animal. For purposes of analysis, a four-category scale used for rating behavior was reduced to two categories, "inactive" (asleep, at rest) and "active" (alert, active), which served as empirical counterparts to the state of the animal when asleep and awake. Comparisons of ratings made simultaneously by pairs of observers during the course of several experiments in Series I showed that the ratings made among the three trained observers were highly reliable. From among 42 series, each consisting of 10-22 joint comparisons, 30 series yielded percentage agreements above 90% and 38 series yielded percentage agreements above 80%. Heart rates were computed from a tally of cardiac cycles recorded

during a sampling interval of 9 or 10 seconds with an accuracy of ± 1.5 beats/minute. Behavioral measurements were closely coordinated in time with measurements of heart rate. As a precaution against the possible development of a systematic observer bias over the series of experiments, tabulation and analysis of all data was delayed until the last series was completed.

For purposes of analysis, since no differences among runs within series were apparent upon inspection, the data were combined over all experiments within each series. Statistical analysis for treatment effects was performed on measurements made at each time point in the exposure test sequence. The principal method for analysis of the behavioral data was made by the determination from Crow's tables (39) of the upper limit of the 95% confidence interval for the proportion of control animals rated as "active." Supplementary χ^2 tests (40,41) were also employed. Analysis of variance techniques were applied to the heart rate data in designs which employed the last pre-irradiation heart rate as the concomitant variable (42). This involved either the analysis of variance of algebriac changes in heart rate from pre-irradiation values or, more frequently, the analysis of covariance among regression-adjusted treatment means (43-45).

A preliminary report of some results obtained during the first minute of exposure in Series I and II has been made (46). This report extends these findings to effects observed during and immediately following exposure.

RESULTS

The Pre-exposure State.

The establishment of a stable and reasonably homogeneous physiologic and psychologic state before the start of exposure was essential to the experimental design in order that radiation-imposed alterations would furnish clear implications. A summary of the data from measurements made during the last five minutes before the start of exposure is shown in Table II. For heart rate (all series) and behavior (Series I-III) comparisons were made between measurements from the first four-minute interval and those from the last 0.6-minute interval. For this analysis, data from each animal were combined over adjacent sampling intervals and the mean heart rate and the presence of any "active" behavior rating obtained within the combined interval were used. For heart rate measurements the correlation between intervals, r_w, was found to be high, above + 0.79 for all series. This stability was not found to be dependent upon sub-grouping by dose rate in that the F test of correlations among dose-rate groups yielded $p > 0.25$ in each series. A similar stability between intervals in proportions of animals rated "active", P(A), was found in Series II and III. The animals in Series I showed a slight last-minute trend toward the inactive state, which was statistically detectable according to McNemar's test of correlated change in proportions ($\chi^2 = 7.20$; $p < 0.01$ for DF = 1). This shift towards the

conditioned state of sleep was equally evident among the dose-rate subgroups ($\chi^2 = 0.48$; $p > 0.70$ for DF = 2).

Prior to exposure a difference in mean heart rate was found between active and inactive animal groups in Series I (Table II). Advantage was taken of this source of heterogeneity by subdividing the series, for purposes of subsequent analyses, into "initially inactive" and "initially active" sub-series. No special selection by "reaction types" was involved by this sub-division since control rats in the intially active sub-series returned to sleep within minutes and were indistinguishable thereafter from initially inactive controls.

Fig. 1 shows the distribution of animals by series on the heart rate measurement for the last pre-irradiation interval. Clearly evident is the effect of the presence or absence of previous training and of restraint in establishing distinguishable states upon which irradiation was then imposed. Among the adapted series the adrenalectomized animals (Series III) displayed a chronic tachycardia, but were otherwise indistinguishable in behavior and appearance from normal animals.

The Initial Reactions to X-ray Exposure.

Figure 2 summarizes the results for the adapted normal animals of Series I that were asleep at the start of exposure (initially inactive sub-series). The analysis was made by dose-rate group of the relative incidence of "active" behavior (upper) and of the change in co-variance

adjusted mean heart rate (lower) for the first sampling interval of 12 seconds (0.1 min.) and the following 30 minutes. In this figure, as in all subsequent figures, the upper limit of the 95% confidence interval (x) for the behavioral rating and of the standard error limits for the heart rate mean (vertical marker) are shown for the control group. Both dose-rate groups showed equivalent incidences of arousal within this first interval ($p < 0.02$) unaccompanied by any change in heart rate. During the middle portion of the first minute (0.5 min.), the group exposed at the rate of 1.9 r/sec exhibited a further increase in the incidence of arousal, but now accompanied by a marked acceleration in heart rate. By the end of the first minute, this group, and also the lower dose-rate (0.25 r/sec) group, appeared to have completed the initial arousal reaction to exposure to X-rays and were returning to their trained quiescent state.

A sham-exposure test was made on some animals at least 30 minutes before the exposure test to determine whether these reactions could be attributed to stimulus artifacts associated with the start of exposure. For this test the X-ray tube was turned off but all other stimulation conditions were the same. Fig. 3 shows the results for initially inactive animals. For the sleeping animal, procedural operations at the start of exposure produced no apparent stimulation. The results of the sham-exposure tests in the other series indicated, likewise, that initial reactions to X-rays could not be attributed to

stimulus artifacts associated with the start of exposure.

Visual stimulation with X-rays could have occurred since these rats were sleeping with eyes closed and, therefore, were partially dark adapted. However, as shown in Fig. 4, ophthalmectomized rats (Series II) that were initially inactive and exposed at the higher dose rate of 1.9 r/sec not only showed as rapid a response as sighted animals, but also exhibited the more intense form of reaction, which involved an immediate accleration in heart rate. Within the first sampling interval the initially inactive blinded animals displayed an average increase of 23.7 (σ_M = 6.8), while initially inactive normal animals from Series I showed an average increase of only 4.5 (3.3) beats/min. The blinded animals that were initially active also showed the reaction with an average increase of 27.0 (3.2) beats/min. The analysis of variance among these mean increases yielded F = 8.84 ($p < 0.005$ for 2 and 15 DF's).

As may be seen in Fig. 5 adrenalectomized animals that were initially inactive failed to show any reaction to exposure at the high dose rate during the first sampling interval but did show evidence of a behavioral arousal and an acceleration in heart rate by the end of the first minute. While the reaction appears to have been delayed, in contradistinction to the reaction of normal rats asleep (Fig. 2) and ophthalmectomized rats (Fig. 4), the magnitude of the response was at least as great. Initially active adrenalectomized animals that were exposed failed to show similar evidence of stimulation.

No clear pattern of heart rate reactions was apparent in normal animals that were not asleep at the start of exposure (initially active sub-groups of Series I, Fig. 6; Series IV, Fig. 7). However, a transitory increase in heart rate was evident during the first minute of exposure in the active, restrained group (Series V, Fig. 8).

The Subsequent Reactions During Continued X-Ray Exposure.

Following the initial arousal reaction, the initially inactive normal rats which were exposed at the lower dose rate (0.25 r/sec.) for 67 minutes, returned to the control level by the end of the first minute and showed no further evidence of wakefulness until the termination of exposure. In contrast, those exposed at the higher rate (1.9 r/sec.) for 9 minutes continued to exhibit wakefulness throughout the residual eight minutes of exposure (Fig. 2). For the period from 2 through 9 minutes the proportion of "active" ratings in two or more adjacent observations was 0.17, 0.18 and 0.60 for control, low and high dose-rate groups, respectively ($\chi^2 = 8.98$; $p < 0.02$ for DF = 2). This behavioral reaction to continued exposure was closely paralleled during this period by the heart rate measurements. Only in the initial sampling interval of 12 seconds was there a failure of correlation between the two variables. The reactions displayed during the residual period of exposure, just as during the first minute, were related to the dose rate since, at comparable accumulated doses, the low dose-rate group failed to exhibit any additional reactions after the first 12-second interval.

Comparable evidence for the occurrence of reactions during continued exposure is even more clearly displayed in the initially active sub-series (Fig. 6). The control and low dose-rate exposure groups settled to the sleep state in accordance with their previous training, but in contrast, the high dose-rate group exhibited upward inflections at 3 minutes (340 r) on heart rate measurements and at 4 minutes (460 r) on behavioral measurements. Again, as with the initially inactive sub-series, this reaction during the residual period of exposure is related to the dose-rate since the low dose-rate group failed to exhibit comparable doses beyond 25 minutes (375 r). The transient behavioral response which was exhibited by the low dose-rate group after 10 minutes of exposure (150 r) was unreliable statistically. Since animals exposed at the higher dose-rate in both sub-series of Series I showed evidence of excitatory effects of irradiation during continued exposure these reactions were largely independent of the state of the animal at the start of exposure.

Although ophthalmectomized animals had shown a more marked initial reaction than had normal animals, they failed to show continued wakefulness or a heart rate response during the residual 8 minutes of exposure (Fig. 9). The similarity between exposed and shielded blinded animals during this period was marked in that in 7 out of 8 tests between co-variance adjusted mean heart rates the F ratios were less than unity. Adrenalectomized rats (Fig. 10) also failed to show a

continuation of the initial elevation in heart rate during exposure; while in behavior they displayed only slight evidence for continued wakefulness. No evidence for X-ray induced excitation was obtained during this interval from heart rate measurements in normal rats that were not previously conditioned to sleep (Fig. 7) or that were actively restrained and in an excited state during exposure (Fig. 8).

Response With Termination of X-ray Exposure

Adapted normal animals exposed at the rate of 1.9 r/sec for 9 minutes continued to displayed reactions in the period immediately following termination of exposure. This occurred in both initially active and inactive sub-groups of Series I (Figs. 2,6). Over the first three measurements following exposure at the higher dose rate (10 to 20 min), 50% and 13% of the high and low dose-rate groups, respectively, received two or more "active" ratings ($\chi^2 = 7.16$; $p < 0.01$ for DF = 1). By 20 minutes after the end of exposure, the high dose-rate animals had returned to the quiescent state concurrently exhibited by the lower dose-rate group. Animals exposed at the lower dose rate of 0.25 r/sec for 67 minutes also differentially exhibited wakefulness for a short period following termination of exposure. In a comparable analysis of behavior over the first three measurements following exposure at the lower dose rate (70 to 90 min), 87% and 55% of the low and high dose-rate groups, respectively, received two or more "active" ratings ($\chi^2 = 5.75$; $p < 0.02$ for DF= 1) and thereafter

the behavior of the low dose-rate group rapidly approached and became nearly identical with that displayed by the higher dose-rate group.

Ophthalmectomized animals exhibited a transient response following termination of exposure on both measures (Fig. 9). The reaction was more apparent in these animals since they showed no evidence of excitation during the terminal minutes of exposure. Adrenalectomized animals also exhibited the transient heart rate response (Fig. 10), although less reliably. As with their initial reactions to exposure, the response was delayed in its first appearance. Non-adapted normal rats showed an elevation in heart rate, absent during the terminal minutes of exposure, which appeared immediately following termination of exposure and was still present at 30 minutes (Fig. 7). Only in restrained, excited animals (Fig. 8) was there a lack of response with the termination of irradiation.

DISCUSSION

It is evident that ionizing radiation can act in a manner quite analogous to a stimulus in that it elicits an arousal reaction from sleep. Observations under sham exposure conditions demonstrated that this reaction could not be attributed to stimulus artifacts associated with the procedure of exposure. Radiation was effective during the sleep state; a condition in which the animal is considered to be relatively insensitive to stimulation (47-49). Arousal from sleep depends upon the relatively slow facilitation (amplification)

mechanisms of the ascending portions of the extra-lemniscal (reticular) system of Magoun (50,51). Since behavioral and heart rate measurements reflect terminal events in slow effector systems, the neurophysiologic events initiated by X-ray exposure must have occurred very early within the first sampling interval of 12 seconds. The rapid appearance of an arousal reaction following the start of exposure to X rays tends to rule out stimulation through abscopal effects at sites remote from nervous tissue, but is consistent with the thesis that ionizing radiation can stimulate the nervous system directly.

The intensity of the initial reactions was dependent upon the dose-rate of exposure. Exposure at the dose rate of 0.25 r/sec elicited only a mild, transient arousal reaction, whereas a dose rate of 1.9 r/sec produced a reaction which was sustained longer, affected more animals, and involved additional sub-cortical regions as reflected by the acceleration in heart rate. The more intense form of the reaction was not dependent upon total exposure dose, since it was absent in the low-intensity exposure group at comparable accumulated doses.

The arousal response appears to be a very sensitive reaction to X-ray stimulation. The doses accumulated by the end of the first interval of 12 seconds were 3 and 23 r, respectively, for the low and high exposure intensities. This initial reaction to X-ray stimulation in the rat, both in latency and in radiosensitivity, is comparable to the most sensitive of the many reflex-like responses found to occur

in invertebrates (29,30). Detection of stimulation in the present study is, of course, dependent upon the concurrent state of the animal. The effects were not dependent in any simple manner upon the state of the nervous system during sleep, since reactions were also observed in restrained animals and in initially active ophthalmectomized animals.

Although X rays act in the manner of a stimulus, its mode of action is less certain. There is no known specific "radiation receptor", and only the visual (photo-chemical) receptor system has been shown to be sensitive to ionizing radiation at energy levels at all comparable to those for the adequate stimulus of light (18,19). Many of the prompt behavioral responses by invertebrates to ionizing irradiation are of a form normally elicited by light (29,30,32,52) and therefore may be produced through stimulation of photo-chemical systems. In the mammal, EEG responses have been reported to occur immediately following the start of irradiation (53), even within the first second during gamma-ray (Co^{60}) exposure of rabbits at dose rates of 2.5 r/sec or more (54). However, these measurements might reflect the central effects of retinal stimulation since the visual system was intact and no tests of possible direct visual stimulation by radiation were imposed.

The extent to which X-ray stimulation of the visual system in normal animals may play a role in the present observations has not

been determined. Asleep and with eyes closed, the rats in Series I were at least partially dark adapted, so that exposure, even at the low intensity of 0.25 r/sec, may have elicited a response to visual stimulation. However, visual stimulation, although possibly present, cannot account for all initial reactions, since similarly trained animals without retinas exhibited the intense form of arousal within the first interval of 12 seconds at the intensity of 1.9 r/sec.

The pattern of initial reactions in blinded rats furnishes a comparison of interest with the reaction pattern in sighted animals. Although exposed at the same intensity, the initial reaction by blinded rats involved cardiac acceleration, which was absent in the normal animal at the earliest test point. The initial absence of a cardiac response in sighted rats could result if visual stimulation exerted a transient inhibitory effect on the excitability of the reticular system to the non-visual mode(s) of X-ray stimulation. Such corticofugal inhibitory systems have been invoked to account both for "gating" of sensory influx to the CNS (55-58) and selective attention (51). Specifically, Wada (59) has demonstrated inhibitory effects of retinal stimulation at various sub-cortical sites, including the hypothalamus. In the present study, sensory deprivation, limited to the visual mode, could results in release from cortical inhibition and produce thereby greater excitability through non-visual mode(s) of stimulation.

The non-visual mode(s) for stimulation by X rays, as demonstrated in blind animals, can only be conjectured. However, some non-visual receptor systems can be reasonably eliminated as possible modes. Tobias, et al (60), have demonstrated a standard blink reflex in the rabbit in which the radiation by heavy ions was limited to the corneal layer containing fibers endings. The threshold intensity for this response system was 10,000 rad in a 2 msec pulse, which is several million times greater than that required in the present study. Receptor systems which involve spike generation in bare fibers, without pre-synaptic receptor amplification for the generation of "receptor potentials" (61), might be expected to show a similar level of sensitivity to ionizing radiation. This could conceivably exclude from consideration many sensory systems, including pain, touch, possibly skin temperature (62), and, perhaps, many mechanoreceptors. Receptors more likely to be directly stimulated by ionizing radiation would be those chemoreceptors which involve radiosensitive biochemical systems at the transduction or early amplification stages of receptor function. This would occur in a manner analogous to that suggested by Lipetz (19) to be the case for the photochemical receptor processes in the retina. Indirect evidence for non-visual, chemoreceptor sensitivity is provided by the presence in some invertebrates, e.g. the ant, of responses to irradiation which normally are elicited by chemical stimuli (30).

The radiation stimulus action need not be limited to sensory systems but could involve alterations of synaptic junctions as well. Long ago, Toyama (63) made such a proposal in his investigations of cardiovascular effects with irradiation of peripheral and central ganglia. Several theories for direct nervous system effects have been advanced recently. As an extension of an enzyme-release theory (64), the rapid release or liberation of neurohormones, particularly amines, was proposed by Brinkman (65) to account for prompt reactions. These substances could conceivably stimulate the CNS secondarily through effects on peripheral systems. This indirect process of stimulation, however, would be unlikely to occur with sufficient rapidity to produce the relatively slow reaction of arousal within 12 seconds following the start of exposure. However, labile forms of several amines, including serotonin, are present in the brain with the highest concentrations found in the hypothalamus and reticular formation (66). The adrenergic components of the reticular system are directly sensitive to a number of catecholamines (67) whether originating peripherally from post-ganglionic sympathetic effector sites (68) and the adrenal medulla (69,70), or from local release within the brain stem (68,71). Accordingly, radiation-induced neurohormonal release from neurovesicles located in synaptic regions in brain tissue could occur immediately and thus effect central activity. Several mechanisms for direct alterations in cell membranes by irradiation have also been

proposed for neural stimulation. Both the direct electrical effect on the membrane potential by ion formation (31,72) and the effect of ionization on metabolic processes (65,73,74), especially the "sodium-pump", have been suggested for high-intensity radiation effects. Hug has proposed (31) that irradiation at low intensities may directly, and reversibly, affect the macromolecular layers of the membrane or, alternatively, that neurochemical processes are effected which then act physiologically on the cell membrane.

It is conceivable that penetrating ionizing radiation acts in the manner of a "distributed stimulus" in that the energy transfer with irradiation occurs nearly instantaneously throughout large masses of nervous tissue. Its effectiveness as a distributed stimulus may depend upon differential density of sensitive structures, the functional organization, and also the momentary state of excitability of those portions of the nervous system that are exposed. The arousal reactions to radiation are similar to the mild reactions that accompany spontaneous arousal from sleep, and that are normally associated with relatively slight changes in the tonic, autochthonous activity of the reticular system (68). Minute alterations induced by radiation in each of a great many synaptic regions, as postulated by a volume stimulus conceptualization, could produce similar disturbances. Detection of the disturbance would depend upon the reticular system facilitating (amplifying) the consequences of the initial effect.

Volume effects in other ganglia, both central and peripheral, might also produce alterations in influx to the reticular system through its manifold connections (75,76) and, thereby, produce prompt activation of the CNS and behavioral arousal.

The action of radiation which produced the initial activation may be expected to continue with the continuation of exposure. However, other sources of stimulation could arise and complicate the pattern of both behavioral and heart rate responses over time. Such sources of stimulation may include the effects of irradiation on peripheral systems, particularly in smooth muscles (30,31), in the gastrointestinal system (33,77), and from the diffuse release of neurohormones (64,65) and various toxic substances from injured cells (21,64,78,79). Immediately following a 4 to 11-minute exposure (200r, 400r) of cats, Gangloff and Haley (5) showed that changes in cortical and sub-cortical electrographic measurements occurred in correspondence to alterations in behavior. More recently, Gangloff (8) reported that the rate of hippocampal spiking was altered in the rabbit during exposure of the head to 400r. In the present study, continued activation in adapted animals during exposure at the high dose rate very likely reflects the effect of these additional sources of stimulation.

A short period of excitation followed the termination of exposure to the lethal, 1,000 r dose in all series except that which involved restrained animals. As displayed in the behavior of adapted

normal animals, excitation occurred following exposure at both dose rates. Groups in which excitatory effects were not displayed during the last minutes of exposure exhibited this reaction as a distinct transitory response in behavior and/or heart rate in the immediate post-exposure period. Although this reaction may reflect an "off" phenomenon, possibly associated with a release from an inhibition induced during exposure, it may also be related to the injurious effects of the accumulated exposure dose.

SUMMARY

Whole-body exposure to 250 kvp X rays was found to have an immediate stimulative effect on the nervous system of the adapted, unanesthetized adult rat. Exposure at a low dose rate (0.25 r/sec) produced a transitory arousal from sleep within the first 12 seconds (accrued dose of 3 r). At a higher dose rate (1.9 r/sec) this initial reaction increased in scope and, by 30 seconds, included also an acceleration in heart rate as well. Only animals exposed at the higher dose rate exhibited evidence of excitation during the residual period of exposure to a 1,000 r total dose. Accordingly, the intensity of the reaction during exposure depended upon the dose rate rather than the total dose. A transient excitatory effect at the termination of exposure was indicated by the occurrence of behavioral wakefulness for a period of minutes following exposure at both dose rates. The excitatory effects of irradiation were not

dependent upon adrenal function since adrenalectomized animals showed a sequence of reactions comparable to that shown by normal animals but with longer latencies. Stimulation through radiosensitive mechanisms apart from the visual receptor system was indicated since ophthalmectomized animals exhibited both behavioral and heart rate responses within seconds after the start of exposure. Some possible modes for the action of ionizing radiation as a stimulus to the nervous system are discussed.

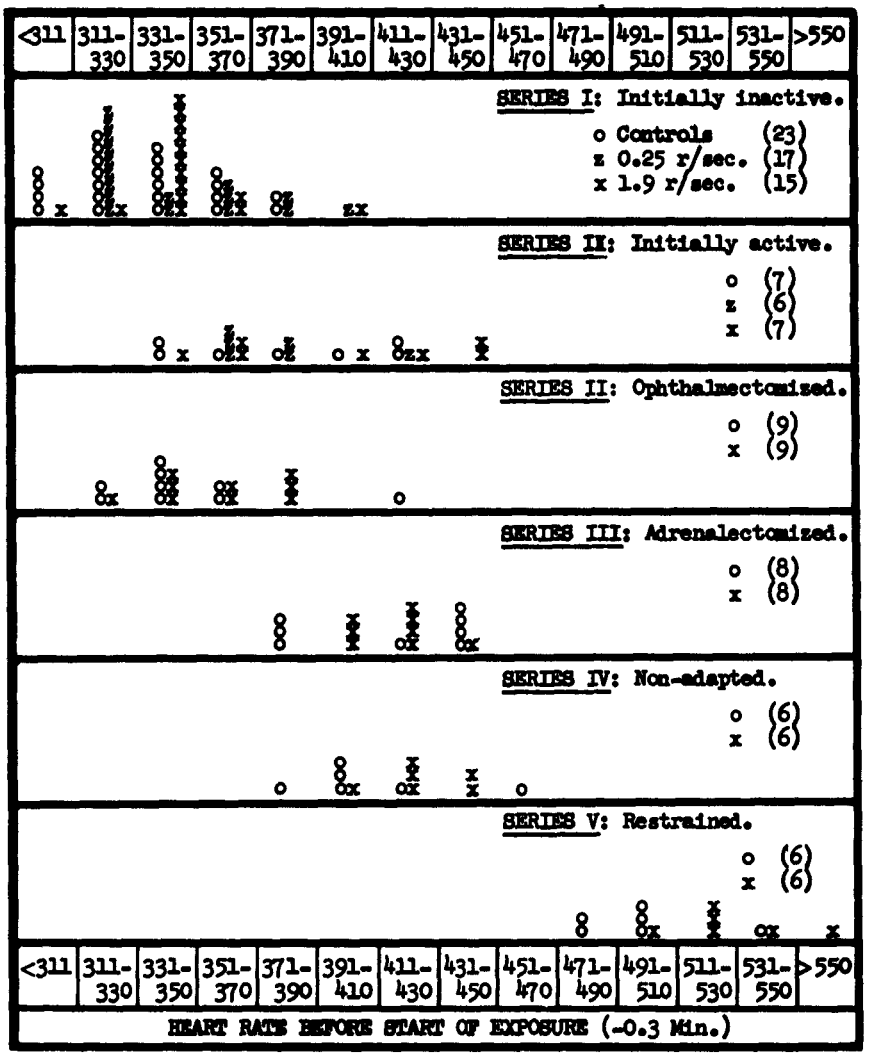

FIG. 1. Distribution of rats on heart rate measurements (beats/min.) made during the last pre-irradiation interval (-0.6 to 0.0 min.) by dose-rate groups within each series.

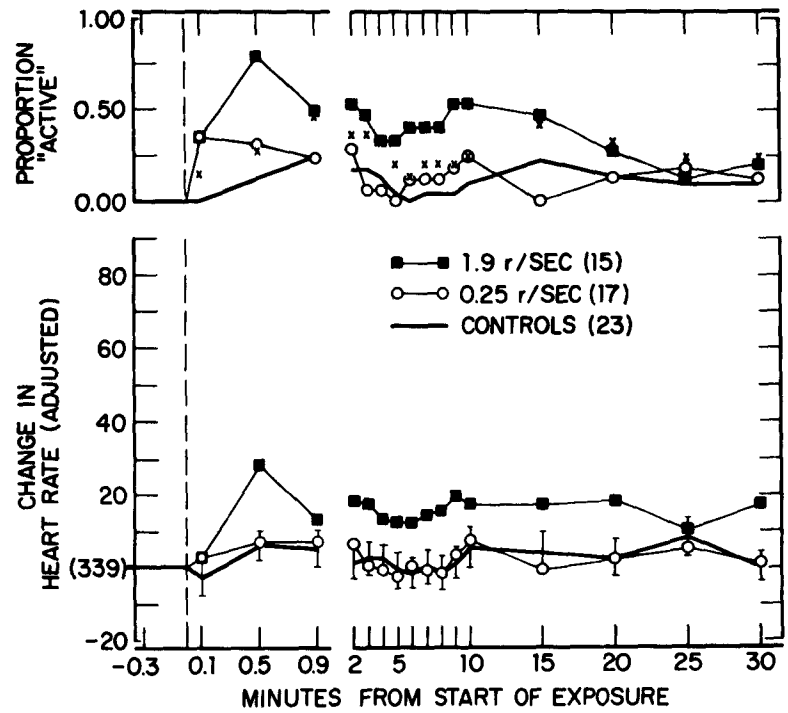

FIG. 2. Alterations after the start of exposure to X rays in the relative incidence of active behavior (upper) and mean heart rate (lower) in initially inactive rats (Series I). Mean heart rates were adjusted in co-variance analysis and graphed as the difference value from the pooled pre-irradiation mean. The upper 95% confidence interval limit on behavior (x) and the standard error limits on heart rate (vertical marker) are indicated for the control group.

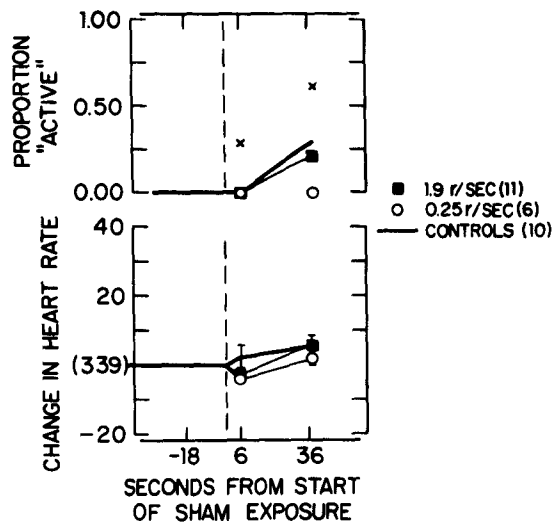

FIG. 3. Behavior and heart rate responses during the sham-exposure test in initially inactive rats (Series I). Figure notations as in Fig. 2.

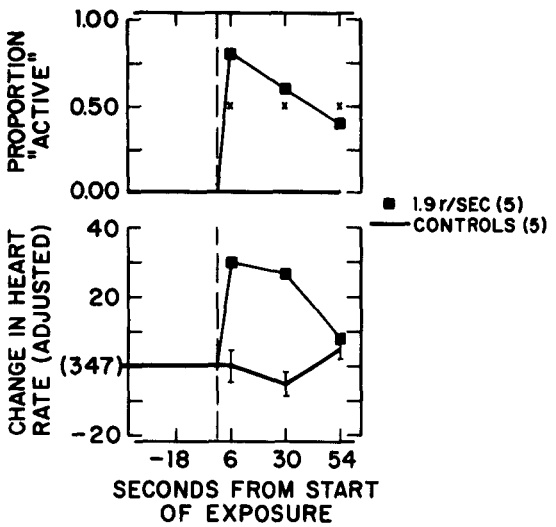

FIG. 4. Immediate changes in the relative incidence of active behavior (upper) and mean heart rate (lower) in initially inactive rats that were subjected to bilateral ophthalmectomy a month before the exposure test (Series II). Figure notations as in Fig. 2.

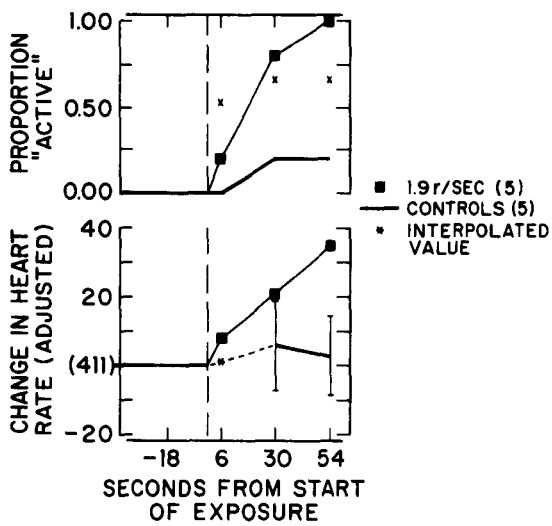

FIG. 5. Immediate changes in the relative incidence of active behavior (upper) and mean heart rate (lower) in initially inactive rats that were subjected to bilateral adrenalectomy a week before the exposure test (Series III). Figure notations as in Fig. 2.

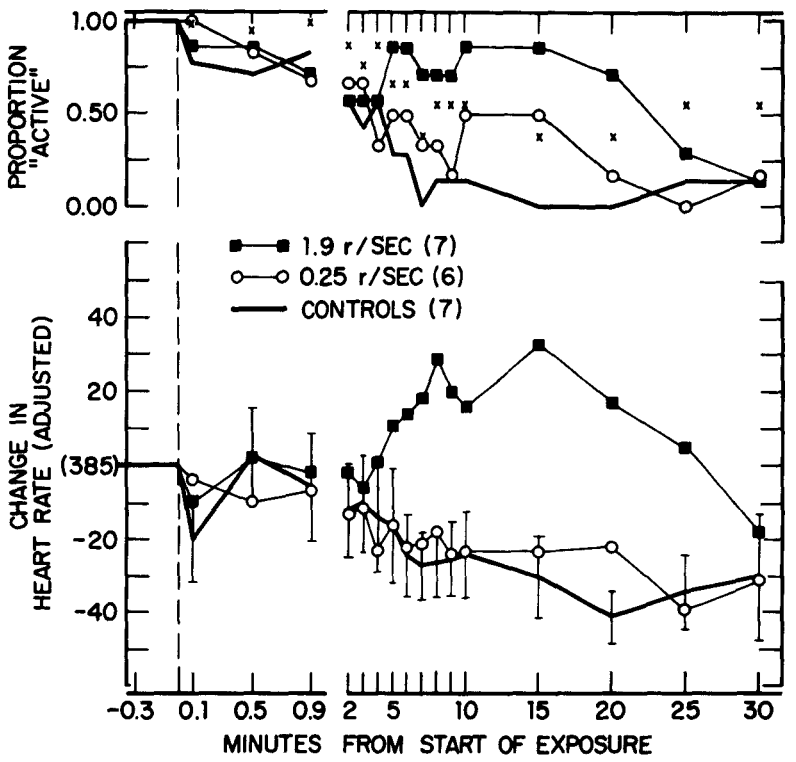

FIG. 6. Alterations after the start of exposure to X rays in the relative incidence of active behavior (upper) and mean heart rate (lower) in initially active rats (Series I). Figure notations as in Fig. 2.

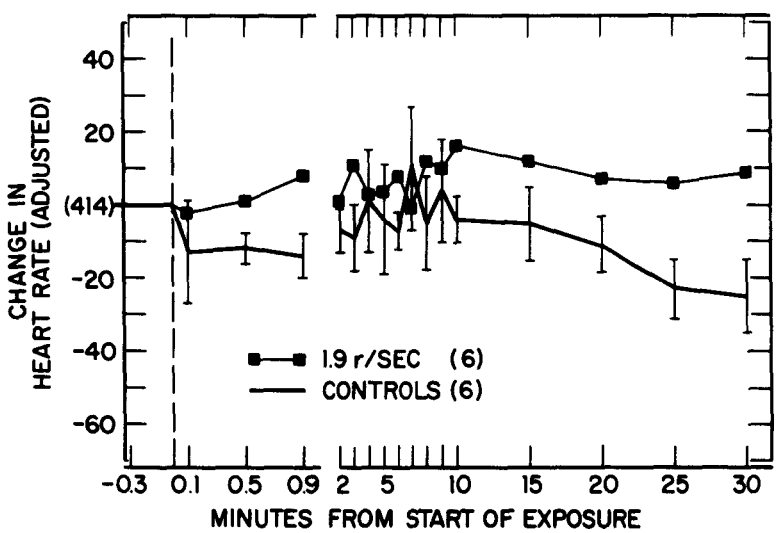

FIG. 7 Alterations in mean heart rate in non-adapted rats following the start of exposure to X rays (Series IV). All animals were rated as active at the start of exposure. Figure notations as in Fig. 2.

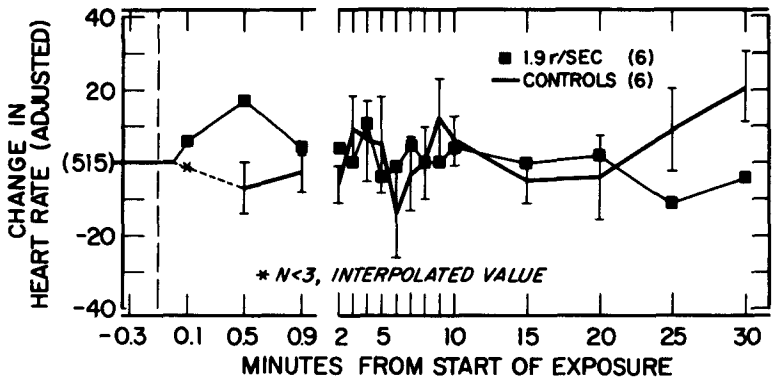

FIG. 8 Alterations in mean heart rate in non-adapted, restrained rats following the start of exposure to X rays (Series V). Figure notations as in Fig. 2.

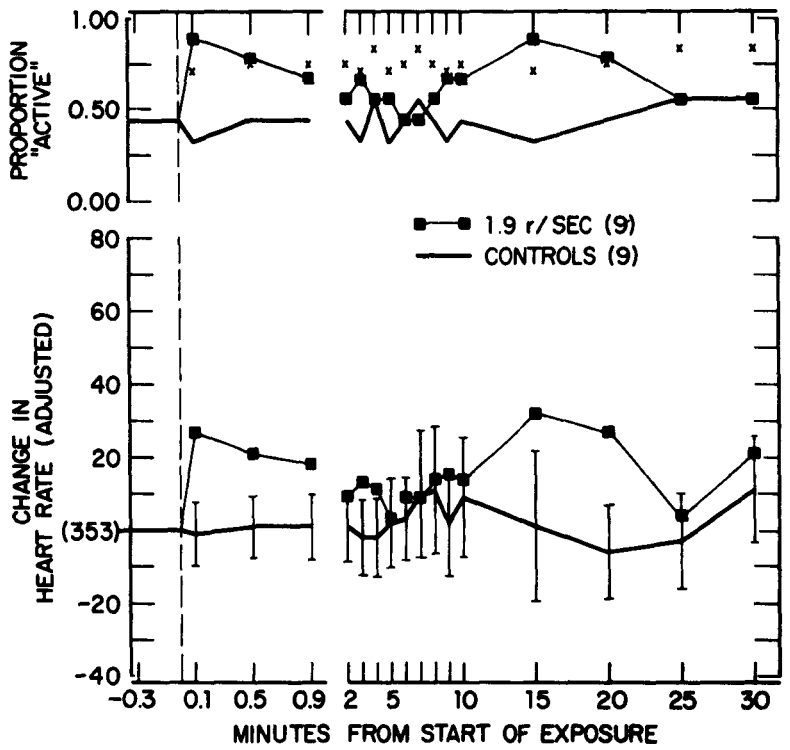

FIG. 9. Alterations after the start of exposure to X rays in the relative incidence of active behavior and mean heart rate in ophthalmectomized, adapted rats (Series II). Figure notations as in Fig. 2.

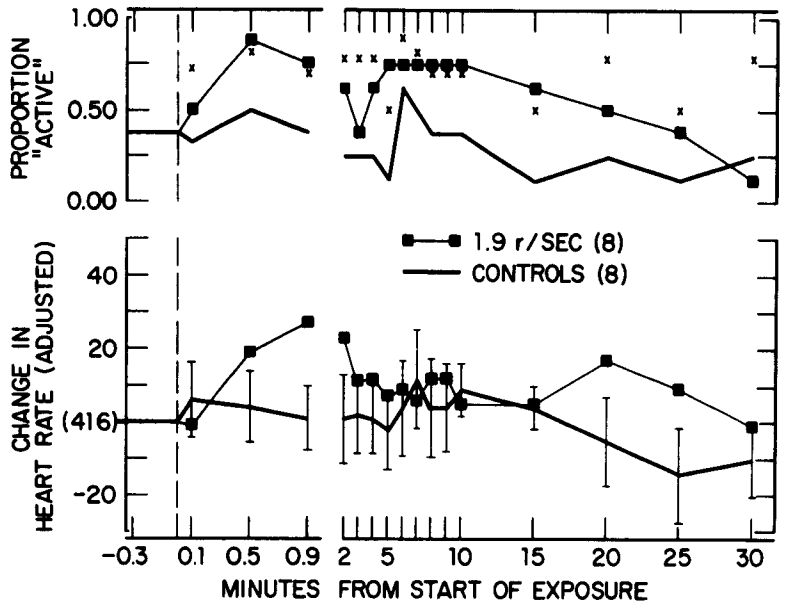

FIG. 10. Alterations after the start of exposure to X rays in the relative incidence of active behavior and mean heart rate in adrenalectomized, adapted rats (Series III). Figure notations as in Fig. 2.

TABLE I. DISTRIBUTION OF ANIMALS IN EACH SERIES BY TREATMENT GROUP

SERIES AND EXPERIMENTAL CONDITIONS	NUMBER OF EXPTS.	TREATMENT GROUPS (r/sec.) CONTROLS (Shielded)	HIGH RATE (1.6-2.0)	LOW RATE (.23-.25)	RANGE IN AGE (Days)	RANGE IN BODY WEIGHT (Grams)
SERIES I: Adapted, normal.	12	30	22	23	59-81	250-374
SERIES II: Adapted, ophthalmectomized[a].	4	9	9	--	68-76	260-330
SERIES III: Adapted, adrenalectomized[b].	3	8	8	--	63-65	271-352
SERIES IV: Non-adapted.	2	6	6	--	59-66	275-368
SERIES V: Restrained.	2	6	6	--	62-68	292-365

[a] Bilateral ophthalmectomy performed at 44 days of age.

[b] Bilateral adrenalectomy performed at 55 days of age and 1% NaCl solution made available continuously thereafter.

TABLE II. HEART RATE AND BEHAVIOR BEFORE THE START OF EXPOSURE BY EXPERIMENTAL SERIES

Mean heart rates (beats/min.) and behavior for two intervals prior to the start of X-ray exposure. The time marker "-3.0" designates the interval from -5.0 to -1.0 minutes and the marker "-0.3" designates the interval from -0.6 to 0.0 minutes. The results of the analysis of variance test on heart rate means between animals rated differentially on behavior as inactive or as active are indicated for the adapted series.

SERIES AND EXPERIMENTAL CONDITIONS	PRE-IRRAD. TIME (MIN.)	COMBINED DOSE-RATE GROUPS				HEART RATE GROUPED BY BEHAVIOR							
		HEART RATE			BEHAVIOR	INACTIVE			ACTIVE			F TEST		
		N	M	(σ)	r_w [a]	P(A) [b]	N	M	(σ)	N	M	(σ)	DF's	F	P
SERIES I: Adapted, normal.	-3.0	75	352	(28)	.90	.43									
	-0.3	75	351	(33)		.27	55	339	(23)	20	385	(36)	1/73	6.76	<.025
SERIES II: Adapted, Ophthalmect.	-3.0	18	352	(32)	.79	.50									
	-0.3	18	353	(25)		.44	10	347	(20)	8	361	(31)	1/16	1.11	ns
SERIES III: Adapted, Adrenalect.	-3.0	16	417	(22)	.85	.31									
	-0.3	16	416	(25)		.38	10	411	(25)	6	425	(25)	1/14	1.10	ns
SERIES IV: Non-adapted.	-3.0	12	408	(17)	.81										
	-0.3	12	414	(22)											
SERIES V: Restrained.	-3.0	12	510	(24)	.80										
	-0.3	12	515	(23)											

[a] The average product-moment correlation (within dose-rate groups) of heart rate between pre-irradiation intervals (-3.0 and -0.3).

[b] Proportion of N rated ACTIVE.

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1	Hq., Army Environmental Hygiene Agency
1	CG., Aberdeen Proving Ground

1	CO, Army Medical Research Laboratory
1	Army Medical Research and Nutrition Laboratory (MEDEN-AD)
1	CO, Army Medical Service Combat Developments Agency
2	Medical Field Service School, Fort Sam Houston (Stimson Lib.)
1	Brooke Army Medical Center (Dept. Prev. Med.)
1	Director, Surgical Research Unit, Fort Sam Houston
1	Director, Walter Reed Army Medical Center
1	Hq., Army Nuclear Medicine Research Detach., Europe
1	CG, Combat Developments Command (CDCMR-V)
1	CG, Quartermaster Res. and Eng. Command
1	Hq., Dugway Proving Ground
3	The Surgeon General (MEDNE)
1	Office of the Surgeon General (Combat Dev.)
1	CG, Engineer Res. and Dev. Laboratory
1	Director, Office of Special Weapons Development
1	CG, Munitions Command
1	CO, Frankford Arsenal
1	CG, Army Missile Command

AIR FORCE

1	Assistant Chief of Staff, Intelligence (AFCIN-3B)
6	CG, Aeronautical Systems Division (ASAPRD-NS)
1	CO, Radiological Health Laboratory Division
1	Director, USAF Project RAND
1	Commandant, School of Aerospace Medicine, Brooks AFB
1	CO, School of Aviation Medicine, Gunter AFB
1	6571st Aeromedical Research Lab., Holloman AFB
1	Radiobiological Laboratory
1	Office of the Surgeon (SUP3.1), Strategic Air Command
1	Office of the Surgeon General
1	CG, Special Weapons Center, Kirtland AFB
1	Director, Air University Library, Maxwell AFB
2	Commander, Technical Training Wing. 3415th TTG
1	Hq., Second Air Force, Barksdale AFB
1	Commander, Electronic Systems Division (CRZT)

OTHER DOD ACTIVITIES

3	Chief, Defense Atomic Support Agency (Library)
1	Commander, FC/DASA, Sandia Base (FCDV)
1	Commander, FC/DASA, Sandia Base (FCTG5, Library)
1	Commander, FC/DASA, Sandia Base (FCWT)
2	Office of Civil Defense, Washington
2	Civil Defense Unit, Army Library
1	Armed Forces Institute of Pathology
20	Armed Services Technical Information Agency
1	Director, Armed Forces Radiobiology Research Institute

AEC ACTIVITIES AND OTHERS

1	Research Analysis Corporation
1	Life Science Officer, AEC, Washington
1	Director, Division of Biology and Medicine
1	NASA, Ames Research Center, Moffett Field
1	Naval Attache, Stockholm (for Commodore Troell)
1	Aerojet General, Azusa
5	Argonne Cancer Research Hospital
10	Argonne National Laboratory
2	Atomic Bomb Casualty Commission
1	AEC Scientific Representative, France
1	AEC Scientific Representative, Japan
3	Atomic Energy Commission, Washington
2	Atomic Energy of Canada, Limited
3	Atomics International
2	Battelle Memorial Institute
1	Borden Chemical Company
3	Brookhaven National Laboratory
1	Chicago Patent Group
1	Colorado State University
1	Columbia University (Rossi)
1	Committee on the Effects of Atomic Radiation
3	Defence Research Member
2	duPont Company, Aiken
1	duPont Company, Wilmington
1	Edgerton, Germeshausen and Grier, Inc., Goleta
1	Edgerton, Germeshausen and Grier, Inc., Las Vegas
2	General Dynamics, Fort Worth
2	General Electric Company, Cincinnati
8	General Electric Company, Richland
1	General Electric Company, St. Petersburg
1	General Scientific Corporation
1	Hughes Aircraft Company, Culver City
1	Iowa State University
1	Journal of Nuclear Medicine
1	Knolls Atomic Power Laboratory
2	Los Alamos Scientific Laboratory (Library)
1	Lovelace Foundation
1	Martin-Marietta Corporation
1	Massachusetts Institute of Technology
1	Mound Laboratory
1	National Academy of Sciences
2	NASA, Scientific and Technical Information Facility
1	National Bureau of Standards (Taylor)
1	National Cancer Institute
1	National Lead Company of Ohio
1	National Library of Medicine
1	New Jersey State Department of Health

1	New York Operations Office
1	New York University (Eisenbud)
1	Office of Assistant General Counsel for Patents
2	Phillips Petroleum Company
4	Pratt and Whitney Aircraft Division
2	Public Health Service, Washington
1	Public Health Service, Las Vegas
1	Public Health Service, Montgomery
1	Sandia Corporation, Albuquerque
1	Union Carbide Nuclear Company (ORGDP)
5	Union Carbide Nuclear Company (ORNL)
1	Union Carbide Nuclear Company (Paducah Plant)
1	United Nuclear Corporation (NDA)
1	U. S. Geological Survey, Denver
1	U. S. Geological Survey, Menlo Park
1	U. S. Geological Survey, Naval Gun Factory
1	U. S. Geological Survey, Washington
1	U. S. Weather Bureau, Washington
1	University of California, Davis
3	University of California Lawrence Radiation Lab., Berkeley
2	University of California Lawrence Radiation Lab., Livermore
1	University of California, Los Angeles
1	University of California, San Francisco
1	University of Chicago Radiation Laboratory
1	University of Hawaii
1	University of Puerto Rico
1	University of Rochester (Atomic Energy Project)
1	University of Tennessee (UTA)
1	University of Utah
1	University of Washington (Donaldson)
1	Wayne State University
1	Westinghouse Electric Corporation (Rahilly)
1	Westinghouse Electric Corporation (NASA)
1	Western Reserve University (Friedell)
25	Technical Information Extension, Oak Ridge

USNRDL

41	USNRDL, Technical Information Division

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BEHAVIORAL AROUSAL AND NEURAL ACTIVATION AS RADIOSENSITIVE REACTIONS by E. L. Hunt and D. J. Kimeldorf 27 February 1963 56 p. tables illus. 79 refs. UNCLASSIFIED

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2. X rays.
3. Dose rate.
4. Radiation effects.
5. Sleep.

I. Hunt, E. L.
II. Kimeldorf, D. J.
III. Title.
IV. MR005.08-5201

UNCLASSIFIED

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